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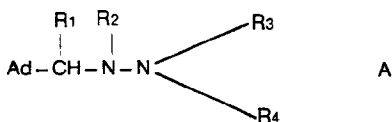
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(54) **Methyladamantyl hydrazines, their preparation and pharmaceutical compositions containing them.**

(57) The invention provides novel 1- or 2-adamantylmethyl hydrazines of the general formula A



Several methods of preparation of the new compounds are described.

The novel compounds according to the invention possess valuable antifungal (human and plant), antiviral, antiprotozoal and antimicrobial properties.

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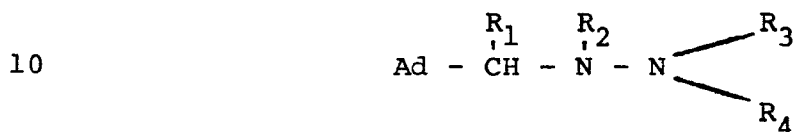
In this formula Ad is 1- or 2-adamantyl, R₁ and R₂ are the same or different and are each hydrogen or a lower unsubstituted or substituted alkyl group of 1-4 carbon atoms; R₃ and R₄ are the same or different and are each hydrogen, an unsubstituted or substituted radical being a lower alkyl group of 1-4 carbon atoms, a lower alkanolic acid radical of 2-4 carbon atoms or a lower alkyl ester thereof, adamantyl, aryl, aralkyl in which the alkyl moiety has 1-4 carbon atoms or an unsubstituted or substituted heterocyclic radical of aromatic character; or R₃ and R₄ together with the nitrogen atom to which they are attached form a cyclic radical of non-aromatic character.

The invention further provides pharmaceutically acceptable acid addition salts of the above compounds.

1 Methyladamantyl hydrazines, their preparation and
pharmaceutical compositions containing them

5 The present invention relates to novel
adamant-1- or -2-ylmethyl hydrazines, to pharmaceutic-
ally acceptable acid addition salts thereof and to
methods of preparing the novel compounds and their
salts.

Specifically the invention provides 1- or
2-adamantylmethyl hydrazines of the general formula A



wherein Ad is 1- or 2-adamantyl, R₁ and R₂ are the same
or different and are each hydrogen or a lower
unsubstituted or substituted alkyl group of 1-4
carbon atoms; R₃ and R₄ are the same or different and
15 are each hydrogen, an unsubstituted or substituted
radical being a lower alkyl group of 1-4 carbon atoms
a lower alkanolic acid radical of 2-4 carbon atoms or a
lower alkyl ester thereof, adamantyl, aryl, aralkyl in
which the alkyl moiety has 1-4 carbon atoms or an
20 unsubstituted or substituted heterocyclic radical of
aromatic character; or R₃ and R₄ together with the
nitrogen atom to which they are attached form a cyclic

1 radical of non-aromatic character; and pharmaceutically acceptable acid addition salts thereof.

The term "lower alkanolic acid or ester radical" refers herein to a radical which is linked
5 to the hydrazine nitrogen atom at one of the non-carboxylic carbon atoms thereof, i.e. at a carbon atom forming part of the lower alkyl moiety of said radical.

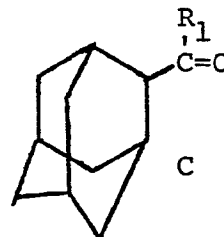
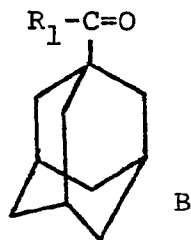
Where R_3 and/or R_4 is a lower alkyl ester of
10 a lower alkanolic acid of 2-4 carbon atoms, the ester forming lower alkyl radical may, for example, be methyl, ethyl, propyl or butyl.

Examples of heterocyclic radicals of aromatic character for which either of R_3 and R_4 may stand are
15 pyridinyl or quinolinyl.

Examples of cyclic radicals formed by R_3 , R_4 and the nitrogen atom to which they are attached are
piperidino, homopiperidino, pyrrolidino, morpholino, thiomorpholino, hydantoino, piperazino or heptamethylene-
20 imino radicals all of which radicals may be substituted.

A compound of formula A in which R_2 is hydrogen can be prepared in accordance with the invention by reacting a compound of either of formulae B and C:

25



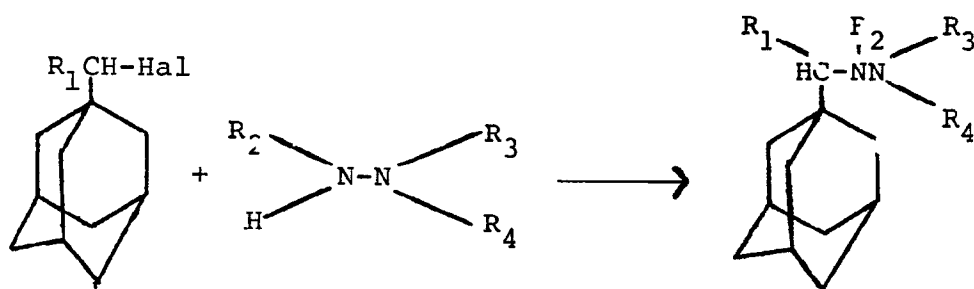
- 1 13. 1-(Adamant-2'-ylmethyl)-2,2-dimethyl-
 hydrazine and pharmaceutically acceptable acid
 addition salts thereof.
- 5 14. 1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)-
 hydrazine and pharmaceutically acceptable acid
 addition salts thereof.
15. (Adamant-1'-ylmethyl)hydrazine and
 pharmaceutically acceptable acid addition salts
 thereof.
- 10 16. 1-(Adamant-1'-ylmethyl)-1-methylhydrazine and
 pharmaceutically acceptable addition salts thereof.
17. 1-(Adamant-2'-ylmethyl)-1-methylhydrazine
 and pharmaceutically acceptable acid addition salts
 thereof.
- 15 18. Ethyl [2-(adamant-1'-ylmethyl)hydrazino]-
 acetate and pharmaceutically acceptable acid addition
 salts thereof.
19. [2-(Adamant-1'-ylmethyl)hydrazino]acetic
 acid and pharmaceutically acceptable acid addition
20 salts thereof.
20. 1,1-Dimethyl-2-(adamant-2'-ylmethyl)-
 hydrazine and pharmaceutically acceptable acid addition
 salts thereof.
21. [1-(Adamant-1'-yl)ethyl]hydrazine and
25 pharmaceutically acceptable acid addition salts thereof.
22. 1-[1'-(Adamant-1"-yl)ethyl]-2-methyl-
 hydrazine and pharmaceutically acceptable acid addition
 salts thereof.

- 1 23. 1-[1'-(Adamant-1"-yl)ethyl]-2-(m-
trifluoromethylphenyl)hydrazine and pharmaceutically
acceptable acid addition salts thereof.
- 5 24. 1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hy-
~~droxyethyl~~)]hydrazine and pharmaceutically acceptable
acid addition salts thereof.
25. 1-(Adamant-1'-ylmethyl)-2-phenethyl-
hydrazine and pharmaceutically acceptable acid
addition salts thereof.
- 10 26. 1-(Adamant-1'-ylmethyl)-2-(p-bromo-
phenyl)hydrazine and pharmaceutically acceptable acid
addition salts thereof.
- 15 27. 1-(Adamant-1'-ylmethyl)-2-[4"-(7"-
chloroquinolinyl)]hydrazine and pharmaceutically
acceptable acid addition salts thereof.
28. 1-(Adamant-1'-ylmethylanino)-2-methyl-
pyrrolidine and pharmaceutically acceptable acid
addition salts thereof.
- 20 29. 1-(Adamant-1'-ylmethylanino)homo-
piperidine and pharmaceutically acceptable acid
addition salts thereof.
30. 1-(Adamant-1'-ylmethylanino)hepta-
methylenimine and pharmaceutically acceptable acid
addition salts thereof.
- 25 31. 1-(Adamant-2'-ylmethylanino)-
pyrrolidine and pharmaceutically acceptable acid
addition salts thereof.

- 1 1-(Adamant-2'-ylmethylamino)piperidine
1-(Adamant-1'-ylmethylamino)thiomorpholine
1-(Adamant-1'-ylmethylamino)hydantoin
1-(Adamant-1'-ylmethyl)-2-butylhydrazine

- 5 By another embodiment adamantylmethyl hydrazines of formula A are prepared by condensation of 1- or 2-haloalkyl adamantane with a hydrazine at elevated temperature and pressure, e.g. in a sealed tube at 150°, in accordance with the following
- 10 Reaction Scheme II in which R₁, R₂, R₃ and R₄ are as in formula A and the haloalkyl group is depicted in the 1-position, Hal being halogen:

Reaction Scheme II

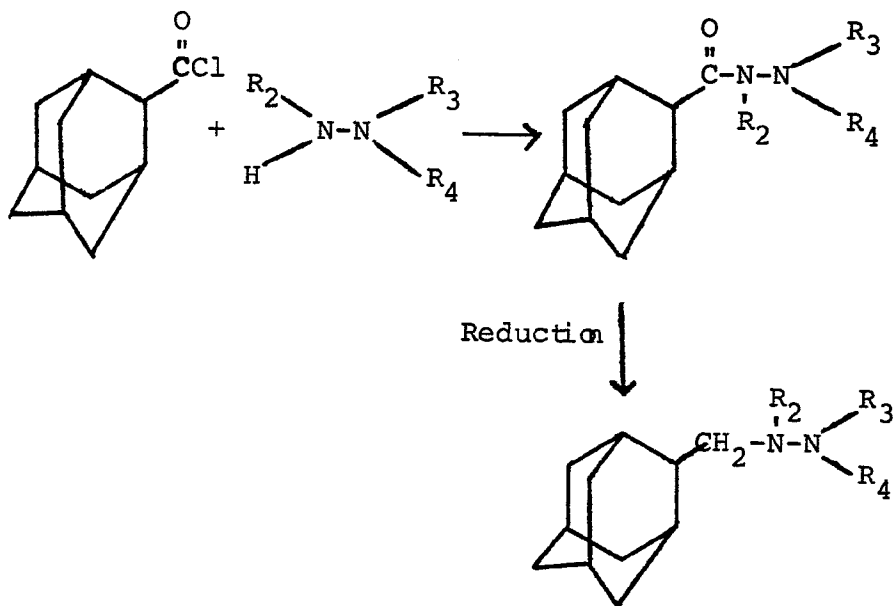


- 15 In this manner (adamant-1-ylmethyl)-hydrazine and 1-(adamant-1'-ylmethyl)-1-methyl-hydrazine were, for example, prepared.

- By yet another embodiment 1- or 2-adamantane carboxylic acid chloride is reacted with a hydrazine
- 20 having at least one free hydrogen and the resulting hydrazide is reduced. This embodiment is shown in the following Reaction Scheme III in which R₂, R₃ and R₄ are as in formula A and the carboxy chloride group is depicted in the 2-position:

1

Reaction Scheme III



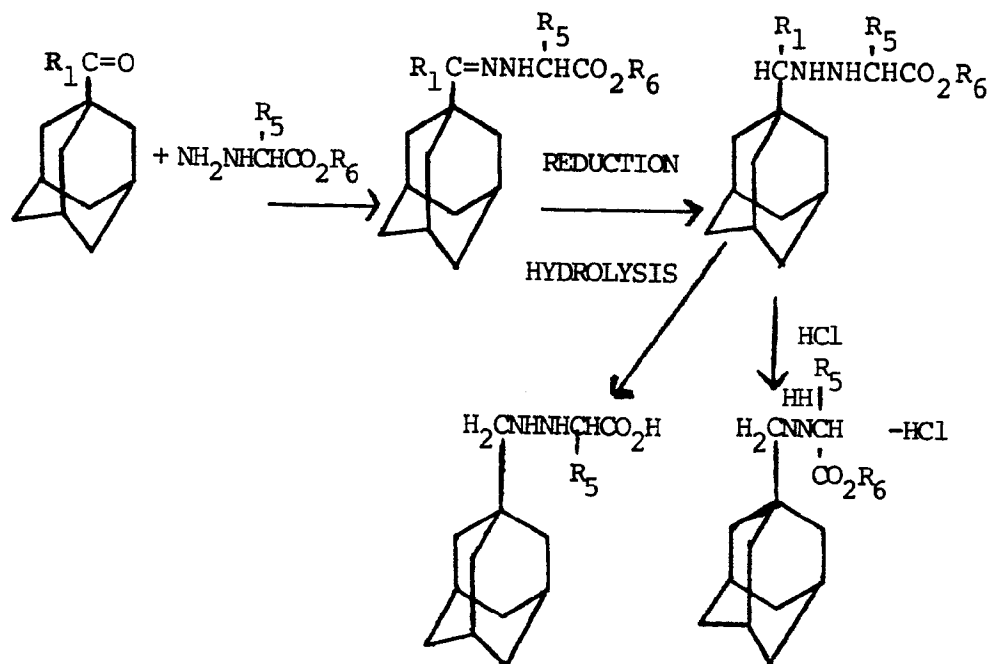
5 For the reduction a hydrogen generating compound such as, for example, lithium aluminium hydride may be used. In this way, using methylhydrazine, 1-(adamant-2'-ylmethyl)-1-methylhydrazine was, for example, prepared.

10 [2-(Adamant-1'-ylmethyl)hydrazino]alkanoic acid esters, their acid addition salts and the corresponding free acids can be prepared in accordance with the invention by a modification of the foregoing embodiment employing a hydrazino acid alkyl ester. This modification is shown in the following Reaction Scheme IV in which R_1 is as in formula A, R_5 is hydrogen methyl or ethyl and R_6 is a lower alkyl and the group $R_1C=O$ is depicted in the 1-position:

15

1

Reaction Scheme IV



For the reduction a hydrogen generating compound such as, e.g., sodium cyanoborohydride may, for example, be used. The hydrolysis is best effected under mild conditions, e.g. by ion exchange or by refluxing with conc. HCl. A suitable ion-exchanger is, for example, the one known by the commercial designation "Amberlite I R 120 (H)".

As representative examples in this way were synthesized:

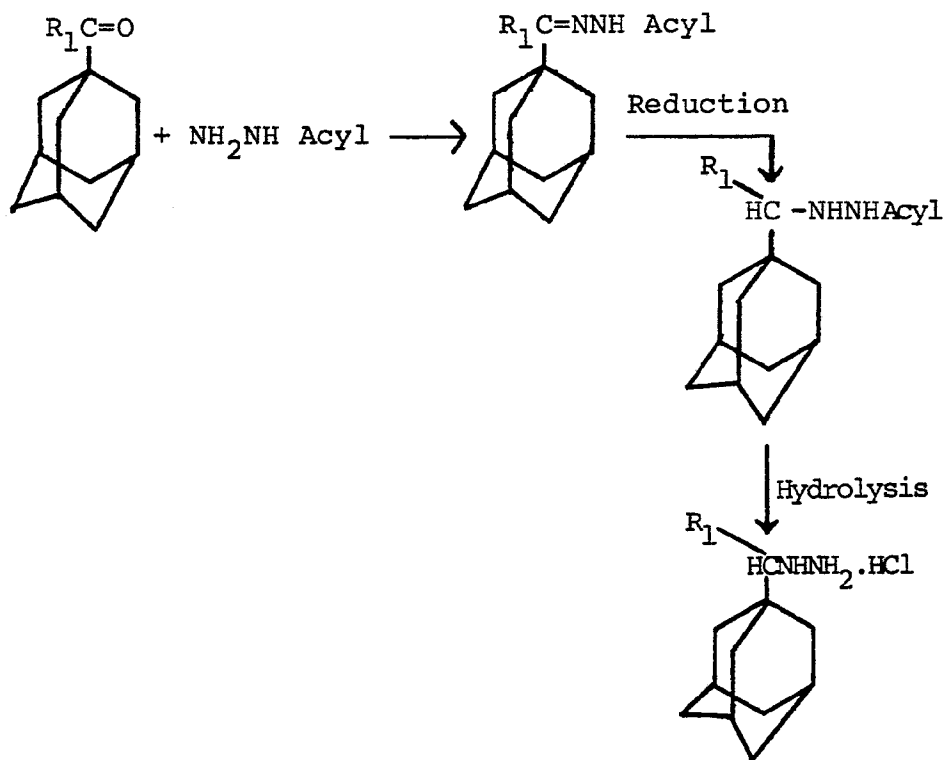
Ethyl [2-(adamant-1'-ylmethyl)hydrazino]acetate
[2-(adamant-1'-ylmethyl)hydrazine]acetic acid, and
 α -[2-(adamant-1'-ylmethyl)hydrazino]butanoic acid.

Attempts at using in the above embodiment free hydrazino acids were unsuccessful, presumably due

1 to their existence as zwitterions which destroys
the nucleophilic character of the hydrazine.

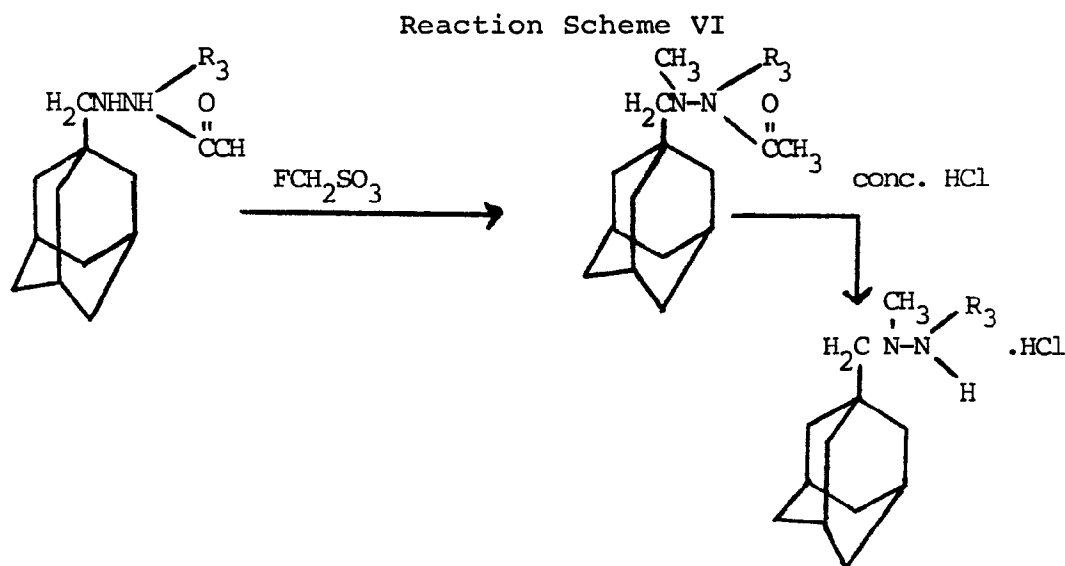
By yet another embodiment for the prepara-
tion of a compound of formula A in which R_1 and R_2
5 are hydrogen, a compound of either of formulae B
and C is reacted with an acyl protected hydrazine in
which the non-protected nitrogen does not bear any
substituent, the resulting protected hydrazone is
reduced and the protected adamantylhydrazine so
10 obtained is hydrolyzed. This embodiment is shown
in the following Reaction Scheme V in which the
 $R_1C=O$ group is depicted in the 1-position:

Reaction Scheme V



1 For the reduction it is again possible to
 use, for example, a hydrogen generating compound
 such as, e.g., sodium cyanoborohydride. For the
 hydrolysis of the acyl group a strong mineral acid
 5 such as, for example, hydrochloric acid can be used.
 In this way (adamant-1-ylmethyl)hydrazine was for
 example, prepared.

By a modification of the above embodiment
 the acylated hydrazine is N-alkylated prior to
 10 hydrolysis. For the alkylation it is possible to
 use, for example, a methyl- or ethylfluorosulfonate.
 The N-alkylated hydrazine is then hydrolyzed as
 above. This modification is shown in the following
 Reaction Scheme VI in which R_2 is as defined in
 15 formula A and the hydrazino moiety is depicted in
 the 1-position and the alkylating agent is methyl-
 fluorosulfonate:



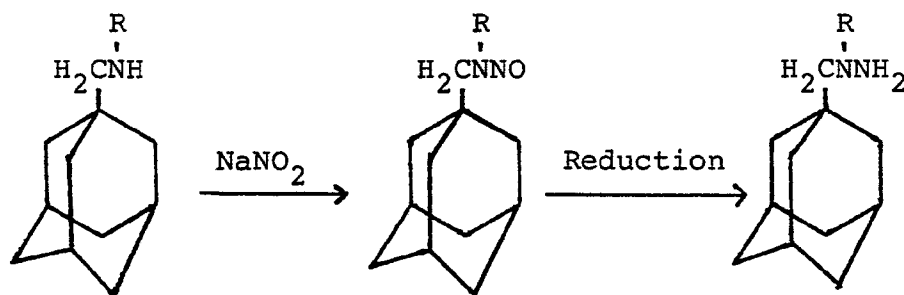
20 In this way 1-(adamant-1'-ylmethyl)-1,2-
 dimethylhydrazine was, for example, prepared.

By yet another embodiment for the preparation
 of a compound of either formulae B and C in which R_3

1 and R_4 are both hydrogen but R_2 is not hydrogen, a
nitrogen-nitrogen bond is formed between a suitable
disubstituted amine and an aminating agent, e.g.
sodium nitrite followed by reduction with a reducing
5 agent, such as lithium aluminium hydride.

For example, (adamant-1'-ylmethyl)isopropyl-
amine was reacted under acidic conditions with
sodium nitrite and the resulting N-nitroso compound
reduced with lithium aluminium hydride to yield
10 1-(adamant-1'-ylmethyl)-1-isopropylhydrazine.
(Scheme VII, R = isopropyl for example).

Reaction Scheme VII

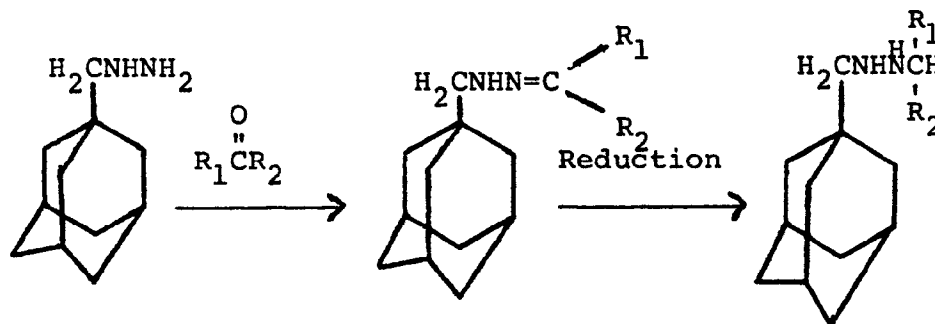


Where in any compound according to the
15 present invention obtained in accordance with any
of the foregoing methods a free hydrogen atom of
the hydrazine moiety is to be substituted, such
substitution may be effected in accordance with
known methods, e.g. alkylation with suitable alkyl-
20 ating agents such as treatment with a powerful base
followed by an alkyl halide. For example, 1-(adamant-
1'-ylmethylamino)pyrrolidine obtained, e.g. in accord-
ance with Scheme I, yields upon treatment with
butyllithium in dry tetrahydrofuran followed by one
25 equivalent of methyl iodide the corresponding
1-[(adamant-1'-ylmethyl)methylamino]pyrrolidine.

1 Furthermore, alkylation of any compound
according to the present invention containing one
unsubstituted nitrogen in the hydrazine moiety may
also be accomplished by condensing said (adamantyl-
5 methyl)hydrazine with a suitable aldehyde or ketone.
The resulting hydrazone may be reduced by any of
the classical reduction methods employed in reaction
Scheme I. For example (adamantyl-1'-ylmethyl)-
10 hydrazine obtained, e.g. in accordance with Reaction
Scheme II, yields upon treatment with acetone, and
subsequent reduction with sodium cyanoborohydride,
the corresponding 1-(adamant-1'-ylmethyl)-2-isopropyl-
hydrazine (see Scheme VIII, $R_1 = R_2 = \text{CH}_3$ for example
only).

15

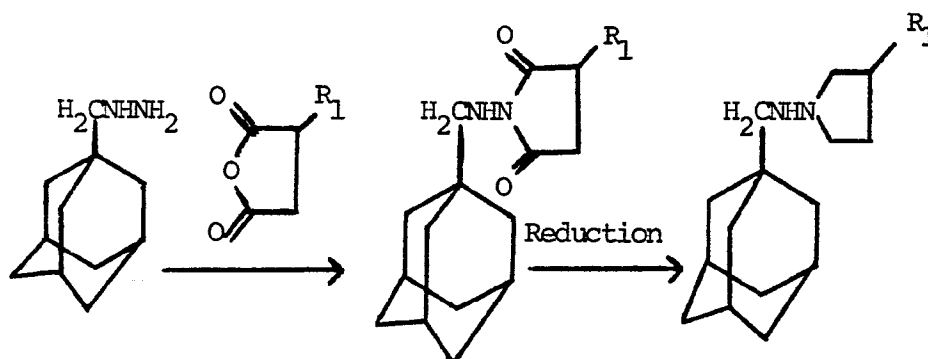
Reaction Scheme VIII



A further modification of the aforementioned alkylation
uses a cyclic carboxylic acid anhydride for example,
as an alkylating agent. The resulting cyclic
20 hydrazide is then reduced in a strong reducing agent
such as lithium aluminiumhydride. For example,
(adamant-1'-ylmethyl)hydrazine was treated with methyl-
succinic anhydride in refluxing toluene with provision
for water removal. The resulting hydrazide was
25 reduced with lithium aluminium hydride to yield 1-
(adamant-1'-ylmethylamino)-3-methylpyrrolidine
(Scheme IX, $R_1 = \text{CH}_3$ for example).

1

Reaction Scheme IX



Quite generally, compounds according to the invention in which the hydrazine moiety is mono-substituted may be converted into di-substituted compounds where the substitution is either on the same nitrogen atom or on different nitrogen atoms and any compound according to the invention in which the hydrazine moiety is di-substituted may be converted by further substitution into the corresponding compound in which the hydrazine moiety is tri-substituted.

In the methods of preparation described hereinbefore the compounds according to the invention are obtained either in the free base form or as acid addition salts. Where a free base is obtained it can be converted into an acid addition salt by reaction with a pharmaceutically acceptable acid as known per se and conversely, where the product first obtained is an acid addition salt and the free base is desired the salt is converted into the free base by reaction with a base, again as known per se.

Furthermore, it is possible to convert an acid addition salt of a compound of formula A into a different one.

1 Novel compounds according to the invention
of the general formula A possess valuable anti-
fungal (human and plant), antiviral, anti-
5 protosoal and antimicrobial properties. Compounds
according to the invention are also active against
infections caused by such viruses as vaccinia,
herpes simplex or influenza or by protozoan
parasites such as leishmania and trypanosoma, or
by microorganisms such as leptospira, and also
10 possess central nervous system (CNS) activity.

For administration to patients the novel
compounds according to the invention are compounded
with pharmaceutically acceptable carriers and, if
desired, with other pharmaceutically active
15 substances and/or pharmaceutically conventional
adjuvants.

The invention also provides compositions
containing each as active ingredient a compound of
formula A together with an acceptable carrier.
20 Where such compositions are pharmaceutical the
carrier must be pharmaceutically acceptable. In
case of veterinary compositions or compositions for
agricultural use the carriers are selected
accordingly.

25 The invention is illustrated by the following
examples to which it is not limited, all temperature
indications being in centigrade.

1

Example 11-(Adamant-1'-ylmethyl)-2-methylhydrazine hydrochloride

A methanolic solution of 1.2 g (7 mmol) of 1-adamantylaldehyde and 1 g (21 mmol) of methylhydrazine was refluxed for 2 hours at which time the volatiles were removed in vacuo. The resulting oil was taken up in ether, washed with water, dried and concentrated to 1.4 g hydrazone which was reduced with an excess of sodium cyanoborohydride in slightly acidified ethanol. After 1 hour the reaction was basified with 10% aq. sodium hydroxide. Solvent evaporation followed by ether extraction, water wash and treatment with hydrogen chloride gave 900 mg (56%) of the title compound.

mp 236 - 238^o (d), (ethylacetate/isopropanol)
nmr (CDCl₃/TFA) δ 2.9 (s, 3H), 2.8 (s, 2H).

Anal calcd for C₁₂H₂₃N₂Cl:

C, 62.49; H, 10.06; N, 12.16; Cl, 15.38;

Found: C, 62.62; H, 10.03; N, 12.55; Cl, 15.65.

Compounds described in the following Examples 2 to 13 and 24 to 36 were prepared by the same method as Example 1, except that 1 equivalent of the appropriate hydrazine derivative was used.

Example 2

25 1-(Adamant-1'-ylmethyl)-2,2-dimethylhydrazine hydrochloride hemi-hydrate

The title compound was obtained in 35% yield by using 1,1-dimethylhydrazine instead of methylhydrazine as in Example 1.

30 mp 284 - 5^o (d), (isopropanol)
nmr (CDCl₃/TFA) δ 3.0 (s., 6H), 2.7 (s, 2H).

1

Anal calcd for $C_{13}H_{26}N_2O_{1/2}Cl$:
C, 61.54; H, 10.25; N, 11.09; Cl, 14.00;
Found: C, 61.21; H, 10.65; N, 11.49; Cl, 13.76.

Example 3

5

1-(Adamant-1'-ylmethyl)-2-benzylhydrazine hydrochloride

The title compound was obtained in 54% yield by using benzylhydrazine instead of methylhydrazine as in Example 1.

10

mp 232-5° (d), (isopropanol/water)
nmr ($CDCl_3$ /TFA) δ 7.3 (s, 5H), 4.3 (s, 2H),
2.8 (s, 2H).

Anal calcd for $C_{18}H_{27}N_2Cl$:
C, 70.43; H, 8.87; N, 9.13; Cl, 11.57
Found: C, 70.26; H, 8.98; N, 9.06; Cl, 11.68

15

Example 4

1-(Adamant-1'-ylmethyl)-2,2-diphenylhydrazine hydrochloride

The title compound was obtained in 48% yield by using 1,1-diphenylhydrazine instead of methylhydrazine as in Example 1.

20

mp 162 - 164° (d), (ethylacetate)
nmr ($CDCl_3$) δ 6.9 - 7.6 (m, 10H), 3.0 (s, 2H)
mass spectrum (m/e) M^+ = 332.

Example 5

25

1-(Adamant-1'-ylmethyl)-2-(*m*-trifluoromethylphenyl)-hydrazine hydrochloride hemi-hydrate

The title compound was obtained in 52% yield by using (*m*-trifluoromethylphenyl)hydrazine instead of methylhydrazine as in Example 1.

30

mp 200 - 203° (d), (ethylacetate)
nmr ($CDCl_3$ /TFA) δ 7.1 - 7.4 (m, 4H);
3.0 (s, 2H).

1 Anal calcd for $C_{18}H_{25}N_2F_3ClO_{1/2}$:
 C, 58.42; H, 6.81; N, 7.88; Cl, 9.60
 Found: C, 58.38; H, 6.78; N, 7.88; Cl, 9.72.

Example 6

5 1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)hydrazine
 The title compound was obtained in 50% yield
 by using N-aminoanthranilic acid instead of methyl-
 hydrazine as in Example 1.

 mp 212 - 3° (d), (ethyl acetate/petroleum
 10 ether).

 nmr ($CDCl_3$ /TFA) δ 3.1 (s, 2H).

 Anal calcd for $C_{18}H_{24}N_2O_2$:

 C, 71.95; H, 8.06; N, 9.32

 Found: C, 72.00; H, 8.31; N, 9.14.

15 Example 7

1-(Adamant-1'-ylmethylamino)pyrrolidine hydrochloride

 The title compound was obtained in 64% yield
 by using 1-aminopyrrolidine instead of methyl-
 hydrazine as in Example 1.

20 mp 260 - 264° (d), (isopropanol)

 nmr ($CDCl_3$ /TFA) δ 2.7 (s, 2H).

 Anal calcd for $C_{15}H_{27}N_2Cl$:

 C, 66.49; H, 10.04; N, 10.34; Cl, 13.11

 Found: C, 66.62; H, 9.93; N, 10.32; Cl, 13.19.

25 Example 8

1-(Adamant-1'-ylmethylamino)piperidine hydrochloride

 The title compound was obtained in 47% yield
 by using 1-aminopiperidine instead of methylhydrazine
 as in Example 1.

1 mp 289 - 291^o (d), (isopropanol)
 nmr (CDCl₃/TFA) δ 2.7 (s, 2H)
 Anal calcd for C₁₆H₂₉N₂Cl:
 C,67.43; H,10.18; N,9.83; Cl,12.47
 5 Found: C,67.69; H,10.50; N,9.64; Cl,12.36.

Example 9

4-(Adamant-1'-ylmethylamino)morpholine hydrochloride
 hemi-hydrate

The title compound was obtained in 45% yield
 10 by using 4-aminomorpholine instead of methylhydrazine
 as in Example 1.

mp 274-276^o (d), (isopropanol)
 nmr (CDCl₃/TFA) δ 2.8 (s, 2H).
 Anal calcd for C₁₅H₂₈N₂ClO_{1.5}:
 15 C,60.87; H,9.54; N,9.46; Cl,12.00
 Found: C,61.10; H,9.37; N,9.80; Cl,11.90.

Example 10

1-(Adamant-1'-ylmethylamino)-4-methylpiperazine
 dihydrochloride hydrate

20 The title compound was obtained in 35% yield
 by using 1-amino-4-methylpiperazine instead of
 methylhydrazine as in Example 1.

mp 286 - 287^o (d), (ethanol)
 nmr (CDCl₃/TFA) δ 2.6 - 4/0 (m, 13H)
 25 Anal calcd for C₁₆H₃₃N₃Cl₂O:
 C,54.19; H,9.40; N,11.85; Cl,20.04
 Found: C,54.52; H,9.12; N,11.18; Cl,20.56.

Example 11

30 1-(Adamant-1'-ylmethylamino)-4-(m-trifluoromethyl-
 phenyl)piperazine hydrochloride hemi-hydrate

The title compound was obtained in 57% yield
 by using 1-amino-4-(m-trifluoromethylphenyl)piperazine

1 instead of methylhydrazine as in Example 1.

mp 261 - 265^o (d), (methanol)

nmr (CDCl₃/TFA) δ 3.9 (S, 8H), 3.0 (S, 2H)

Anal calcd for C₂₂H₃₂N₃ClF₃O_{1/2} :

5 C, 60.21; H, 7.30; N, 9.58; Cl, 8.10; F, 13.00

Found: C, 60.44; H, 7.30; N, 9.62; Cl, 8.22; F, 12.52.

Example 12

1-(Adamant-2'-ylmethyl)-2,2-dimethylhydrazine hydrochloride

10 The title compound was obtained in 30% yield by using 2-adamantylaldehyde and 1,1-dimethylhydrazine instead of 1-adamantylaldehyde and methylhydrazine respectively as in Example 1.

mp 217-220^o (d), (ethyl acetate/methylene chloride)

15 nmr (CDCl₃) δ 3.15 (d, 2H); 2.86 (S, 6H)

Anal calcd for C₁₃H₂₅N₂Cl:

N, 11.45; Cl, 14.52

Found: N, 11.43; Cl, 14.46.

Example 13

1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)hydrazine hydrochloride

20 The title compound was obtained in 55% yield by using 2-adamantylaldehyde and (pyrid-2'-yl)-
25 hydrazine instead of 1-adamantylaldehyde and methylhydrazine respectively as in Example 1.

mp 135 - 140^o (d), (ethyl acetate)

nmr (CDCl₃/TFA) δ 3.33 - 3.60 (d, 2H).

mass spectrum (m/e) M⁺ = 257.

Example 14

(Adamant-1-ylmethyl)hydrazine hydrochloride

30

4.0 g (120 mmol) of anhydrous hydrazine and
2.3 g (12 mmol) of 1-chloromethyladamantane were
introduced into a sealable tube under nitrogen
atmosphere. The tube was sealed and heated at
5 150° for 16 hours. After cooling to room temperature
the contents were suspended in methanol, treated
with a solution 0.5 g of sodium hydroxide in 1.5 ml
of water, and the volatiles removed in vacuo. The
resulting solid was extracted with ether and the
10 solution dried with magnesium sulfate and treated
with hydrogen chloride to give 1 g of the title
compound (38% yield).

mp 256 - 258° (d), (isopropanol)
nmr (CDCl₃/TFA) δ 3.3 (s, 2H)
15 Anal calcd for C₁₁H₂₁N₂Cl:
C, 60.97; H, 9.78; N, 12.94; Cl, 16.37
Found: C, 61.20; H, 9.71; N, 12.85; Cl, 16.77.

Example 15

20 1-Methyl-1-(adamant-1'-ylmethyl)hydrazine hydrochloride
hydrate

The procedure of Example 14 was followed using
methylhydrazine instead of anhydrous hydrazine. The
resulting ether solution containing the 2 possible
condensation products, the title compound and the
25 2-methyl isomer, was stored at about 5° for 4 days. There-
after treatment with hydrogen chloride caused the
title compound to crystallize from the solution in
95% purity (35% yield).

mp 196-197° (d), (ethyl acetate/methylene
30 chloride)
nmr (CDCl₃/TFA) δ 3.05 (s, 3H), 2.95 (s, 2H)

1 Anal calcd for $C_{12}H_{25}N_2ClO$:
 C, 57.90; H, 10.13; N, 11.25; Cl, 14.27
 Found: C, 57.86; H, 10.24; N, 11.09; Cl, 14.12.

Example 16

5 1-Methyl-1-(adamant-2'-ylmethyl)hydrazine
 hydrochloride

 To 7 g of methylhydrazine in 25 ml of ethyl-
 acetate was added 5.4 g of 2-adamantylcarboxylic acid
 chloride in 25 ml of the same solvent. After 15
 10 minutes additional stirring the reaction was washed
 with a solution of ammonium chloride and concentrated
 to 4.5 g of hydrazide. The hydrazide was reduced
 with 1.1 g of lithium aluminum hydride in refluxing
 tetrahydrofuran for 1/2 hour.

15 After cooling the reaction was poured into
 aqueous ammonium chloride and extracted 2 times with
 methylenechloride. The combined organic layers were
 dried over magnesium sulfate and solvent removed in
 vacuo. The resulting oil was dissolved in ether and
 20 treated with hydrogen chloride to give 2.4 g of the title
 compound (40% yield).

 mp 224-6° (d), (ethyl acetate)

 nmr ($CDCl_3$) δ 3.28 (d, 2H), 2.96 (s, 3H)

 Anal calcd for $C_{12}H_{23}ClN_2$:

25 C, 62.47; H, 9.97; N, 12.14; Cl, 15.40

 Found: C, 62.67; H, 9.95; N, 12.10; Cl, 15.10.

Example 17

Ethyl [(2-adamant-1'-ylmethyl)hydrazino]acetate
hydrochloride

30 The procedure of Example 1 was followed using
 ethyl hydrazino-acetate instead of methylhydrazine,
 to give the title compound in 24% yield.

1 mp 188-190^o (d), (ethyl acetate)
 nmr (CDCl₃) δ 4.2 (q, 2H); 4.0 (s, 1H);
 2.9 (s, 1H); 1.3 (t, 3H)
 Anal calcd for C₁₅H₂₇N₂O₂Cl:
 5 C, 59.50; H, 8.92
 Found: C, 59.36; H, 8.70.

Example 18

[2-(Adamantyl-1'-ylmethyl)hydrazino]acetic acid
 hydrochloride

10 The hydrazino ester hydrochloride (3 g) of
 Example 17 was hydrolyzed with 2 g of Amberlite IR
 120 (H) in refluxing water for 5 hrs to give the
 title compound in 25% yield after filtration and
 evaporation of solvent.

15 mp 178-179^o (isopropanol, ethyl acetate)
 nmr (CDCl₃/TFA) δ 4.0 (s, 2H), 3.0 (s, 2H).
 Anal calcd for C₁₃H₂₃N₂O₂Cl:
 C, 56.79; H, 8.45; N, 10.19
 Found: C, 57.00; H, 8.19; N, 9.78.

Example 19

(Adamant-1-ylmethyl)hydrazine hydrochloride

The title compound was also prepared in analogy
 with Example 1 using acetylhydrazine instead of
 methylhydrazine. The acetyl group was cleaved by 2
 25 hours reflux in conc. HCl, giving a product with
 identical properties to those of Example 14
 (58% yield).

Example 20

1,2-Dimethyl-1-(adamant-1'-ylmethyl)hydrazine
 hydrochloride

30 The procedure of Example 1 was followed using
 1-acetyl-1-methylhydrazine instead of methylhydrazine.
 After reduction, the resulting acetylhydrazine was
 treated with one equivalent of methyl fluorosulfonate

1 in methyl acetate at 0°. After stirring for 2 hours
the reaction was poured into 10% aq sodium hydroxide
and extracted with methylene chloride, the solvent
removed and the residue was treated with conc. HCl
5 and refluxed for 1 hour to give the title compound
upon cooling.

mp 176-179° (d), (ethyl acetate)

nmr (CDCl₃) δ 2.8 (s, 3H); 2.7 (s, 3H);

2.6 (s, 2H)

10 Anal calcd for C₁₃H₂₅N₂Cl:

C, 63.75; H, 10.30; N, 11.44; Cl, 14.51

Found: C, 63.81; H, 10.40; N, 11.44; Cl, 14.94.

Example 21

[1-(Adamant-1'-yl)ethyl]hydrazine hydrochloride

15 The procedure of Example 19 was followed using
acetyladamantane instead of 1-adamantylaldehyde to
give the title compound in 26% yield.

mp 212-214° (d), (isopropanol)

nmr (CDCl₃/TFA) δ 2.95 (q, 1H, J = 7Hz),

20 (d, 3H, J = 7Hz).

Anal calcd for C₁₂H₂₃N₂Cl:

C, 62.49; H, 10.06; N, 12.16; Cl, 15.38

Found: C, 62.23; H, 10.03; N, 12.61; Cl, 15.09.

25 Example 22

1-[1'-(Adamant-1"-yl)ethyl]-2-methylhydrazine hydrochloride

A solution of 1.8 g (10 mmol) of acetyl-
adamantane and 600 mg (13 mmol) of methylhydrazine was
30 refluxed in 150 ml of benzene with continuous removal
of water via a Dean-Stark Apparatus.

After 2 1/2 hours the reaction was cooled the
volatiles removed in vacuo leaving 1.7 g oil which was
reduced with 800 mg of sodium cyanoborohydride according

1 to the procedure of Example 1. Treatment of the
resulting ether solution with hydrogen chloride gave
900 mg of the title compound (37% yield).

mp 239 - 241^o (d), (acetone)

5 nmr (CDCl₃/TFA) δ 1.3 (d, 3H)

Anal calcd for C₁₃H₂₅N₂Cl:

C, 63.75; H, 10.30; N, 11.44; Cl, 14.49

Found: C, 63.71; H, 10.60; N, 11.29; Cl, 14.90.

Example 23

10 1-[1'-(Adamant-1"-yl)ethyl]-2-(m-trifluoromethylphenyl)-
hydrazine hydrochloride hemi-hydrate

Following the procedure of Example 5, but using
1-acetyladamantane instead of 1-adamantylaldehyde the
title compound was obtained in 37% yield.

15 mp 198 - 200^o (d), (ethyl acetate)

nmr (DMSO-d₆) δ 1.25 (d, 3H)

Anal calcd for C₁₉H₂₇N₂ClF₃O₁₂:

C, 59.42; H, 7.08; N, 7.29

Found: C, 59.27; H, 6.92; N, 7.06.

20 Example 24

1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hydroxyethyl)]hydrazine
hydrochloride

The title compound was obtained in 42% yield
by using 2-hydrazinoethanol instead of methylhydrazine
25 as in Example 1 except that the resulting hydrazone
was reduced with 50 psi H₂ on 10% palladium on carbon.

mp 194^o (d), (methanol/ethylacetate)

nmr (CDCl₃/TFA) δ 3.4-4.4 (m, 2H), 3.3-3.6
(m, 2H); 3.0 (s, 2H)

30 Anal calcd for C₁₃H₂₅ClN₂O:

C, 59.88; H, 9.60; N, 10.75; Cl, 13.63

Found: C, 59.71; H, 9.74; N, 10.94; Cl, 13.65.

1

Example 251-(Adamant-1'-ylmethyl)-2-phenethylhydrazine
dihydrate

5 The title compound was obtained in 29% yield
by using phenethylhydrazine instead of methyl-
hydrazine as in Example 1.

mp 231-235° (d), (isopropanol/ether)

nmr (CDCl₃/TFA) δ 7.2 (s, 5H); 3.4 (d, 2H);
2.7 (s, 2H)

10 Anal calcd for C₁₉H₃₂N₂O₂:

C, 71.21; H, 10.05; N, 8.74

Found: C, 71.62; H, 10.37; N, 8.27.

Example 26

15 1-(Adamant-1'-ylmethyl)-2-(p-bromophenyl)hydrazine
hydrochloride

The title compound was obtained in 75% yield
by using p-bromophenylhydrazine instead of methyl-
hydrazine as in Example 1.

mp 214-215° (d), (isopropanol/methanol)

20 nmr (CDCl₃/TFA) δ 7.18 (q, 4H); 2.95 (s, 2H)

Anal calcd for C₁₇H₂₄N₂BrCl:

C, 54.92; H, 6.44; N, 7.52; Cl, 9.50; Br, 21.51

Found: C, 54.53; H, 6.37; N, 7.31; Cl, 9.25; Br, 22.02

Example 27

25 1-(Adamant-1'-ylmethyl)-2-[4"-(7"-chloroquinolinyl)]-
hydrazine hemi-hydrate

The title compound was obtained in 17% yield
by using 7-chloro-4-hydrazinoquinoline instead of
methylhydrazine as in Example 1.

30 mp 308-312° (d), (isopropanol)

nmr (CDCl₃) δ 8.6-8.9 (m, 1H), 7.9-8.2 (m, 2H),
7.0-7.4 (m, 2H), 2.7 (br.s., 2H)

1 Anal calcd for $C_{20}H_{26}N_3Cl_2O_{\frac{1}{2}}$:
 C, 61.98; H, 6.73; N, 10.84
 Found: C, 61.52; H, 6.17; N, 10.39.

Example 28

5 1-(Adamant-1'-ylmethylamino)-2-methylpyrrolidine
 hydrochloride

 The title compound was obtained in 58% yield
 by using 1-amino-2-methylpyrrolidine instead of
 methylhydrazine as in Example 1.

10 mp 254-256° (d), (isopropanol/ether)
 nmr (CDCl₃/TFA) δ 3.2-4.0 (m, 3H); 2.6 (s, 2H);
 1.4-2.5 (m, 22H)
 mass spectrum (m/e) M+ = 248 (64), 233 (78),
 135 (65), 133 (100), 107 (38).

Example 29

15 1-(Adamant-1'-ylmethylamino)homopiperidine
 hydrochloride quarterhydrate

 The title compound was synthesized in 43% yield
 by using 1-amino-homopiperidine instead of methyl-
 hydrazine as in Example 1.

20 mp 265° (d), (isopropanol)
 nmr (CDCl₃) δ 2.75 (m, 4H), 2.5 (s, 2H)
 Anal calcd for $C_{17}H_{31}N_2Cl_{\frac{1}{4}}H_2O$:
 C, 67.20; H, 10.20; N, 9.22
 Found: C, 67.24; H, 10.19; N, 9.07.

Example 30

30 1-(Adamant-1'-ylmethylamino)heptamethyleneimine
 hydrochloride

 The title compound was obtained in 16% yield
 using 1-aminoheptamethyleneimine instead of methyl-
 hydrazine as in Example 1, except that the resulting
 hydrazone was reduced with lithium aluminium hydride.

1 mp 285-261^o (d), (isopropanol/ethyl
acetate)
nmr (CDCl₃) δ 3.0-3.6 (m, 4H),
2.7 (br.s. 2H)
5 Anal calcd for C₁₈H₃₃N₂Cl:
N, 8.96
Found: N, 8.81.

Example 31

1-(Adamant-2'-ylmethylamino)pyrrolidine hydrochloride

10 The title compound was obtained in 35%
yield by using 2-adamantylaldehyde and 1-amino-
pyrrolidine instead of 1-adamantylaldehyde and methyl-
hydrazine respectively as in Example 1 except that
the resulting hydrazone was reduced with lithium
15 aluminium hydride.

mp 235^o (d), (ethylacetate)
nmr (CDCl₃) δ 2.8-4.0 (m, 6H)
Anal calcd for C₁₅H₂₇N₂Cl:
C, 66.54; H, 9.98; N, 10.35; Cl, 13.12
20 Found: C, 66.41; H, 9.74; N, 10.04; Cl, 13.12.

Example 32

1-(Adamant-2'-ylmethylamino)piperidine hydrochloride

The title compound was obtained in 20%
yield using 2-adamantylaldehyde and 1-aminopiperidine
25 instead of 1-adamantylaldehyde and methylhydrazine as
in Example 1 except that the resulting hydrazone was
reduced with lithium aluminium hydride.

mp 263-264^o (d), (isopropanol)
nmr (CDCl₃) δ 3.1-3.5 (m, 6H)
30 Anal calcd for C₁₆H₂₉N₂Cl:
C, 67.48; H, 10.19; N, 9.84; Cl, 12.47
Found: C, 67.31; H, 10.35; N, 9.78; Cl, 12.91.

1

Example 331-(Adamant-2'-ylmethyl)-2-(1"-adamantyl)hydrazine hydrochloride hemihydrate

5 The title compound was obtained in 5% yield using 2-adamantylaldehyde and 1-adamantylhydrazine instead of 1-adamantylaldehyde and methylhydrazine as in Example 1, except that the resulting hydrazone was reduced with lithium aluminum hydride.

mp 290-292° (d), (methanol)
10 nmr (CDCl₃) δ 3.1 (d, 2H); 1.5-2.5 (m, 30H)

Anal calcd for C₂₁H₃₆N₂ClO_{1/2}:

C, 70.09; H, 10.01; N, 7.78;

Found: C, 70.26; H, 10.10; N, 8.11

Example 34

15 1-(Adamant-1'-ylmethylamino)thiomorpholine hydrochloride

The title compound was obtained in 38% yield using 1-aminothiomorpholine instead of methylhydrazine as in Example 1.

mp 269-272° (d), (isopropanol/ethylacetate)
20 nmr (CDCl₃/TFA) δ 3.4-3.6 (m, 4H), 2.8-3.1 (m, 4H), 2.7 (br.s. 2H)

Anal calcd for C₁₅H₂₇N₂SCl :

C, 59.50; H, 8.92; N, 9.25; Cl, 11.72; S, 10.57

Found: C, 59.23; H, 8.73; N, 8.91; Cl, 12.00; S, 11.04

25

Example 351-(Adamant-1'-ylmethylamino)hydantoin

The title compound was obtained in 10% yield using 1-aminohydantoin sulfate instead of methylhydrazine as in Example 1.

30 mp 193-194° (d), (isopropanol)

nmr (CDCl₃/TFA) δ 4.5 (s, 2H); 3.2 (s, 2H).

1 Anal calcd for $C_{14}H_{22}N_3O_2$:
 C, 63.59; H, 8.40; N, 15.89
 Found: C, 63.06; H, 8.18; N, 15.67.

Example 36

5 1-(Adamant-1'-ylmethyl)-2-butylhydrazine
 hydrochloride hemi-demi-hydrate

 The title compound was obtained in 39% yield
 using n-butylhydrazine hydrochloride (prepared in situ
 from the oxalate and conc. HCl) instead of methyl-
 10 hydrazine as in Example 1.

 mp 236-240° (d), (isopropanol)
 nmr ($CDCl_3$ /TFA) δ 3.2 (t, 2H); 2.7 (s, 2H)
 Anal calcd for $C_{15}H_{29.5}N_2ClO_{1/4}$:
 C, 64.98; H, 10.64; N, 10.10
 15 Found: C, 64.71; H, 10.38; N, 10.04.

Example 37

α -[2-(Adamant-1'-ylmethyl)hydrazino]butanoic acid
hydrochloride

 A methanolic solution of 1.64 g (10 mmol) of
 20 1-adamantylaldehyde, 1.8 g (10 mmol) of ethyl
 hydrazinobutanoate hydrochloride and 5.6 g (10 mmol)
 of KOH was refluxed for 2 1/2 hrs. The volatiles
 were removed in vacuo and the residue partitioned
 between methylene chloride and water. The organic
 25 layer was dried and concentrated to 3 g of
 hydrazone which was reduced with 750 mg of sodium
 cyanoborohydride. The resulting hydrazino ester was
 hydrolyzed by refluxing in 5 ml of conc. HCl for
 30 min. Evaporation of the volatiles give the title
 30 compound in 75% yield.

 mp 188-190° (d), (isopropanol/ethyl acetate)
 nmr ($CDCl_3$ /TFA) δ 4.0 (t, 1H); 2.9 (s, 2H);
 1.0 (t, 3H).

1 Anal calcd for $C_{15}H_{27}N_2O_2Cl$:
 C, 59.46; H, 8.99; N, 9.25; Cl, 11.73
 Found: C, 59.52; H, 8.81; N, 9.20; Cl, 12.85.

Example 38

5 1-(Adamant-1'-ylmethyl)-1-isopropylhydrazine
 hydrochloride

 A methanolic solution of 3 g (18 mmol) of
 adamant-1-ylmethylamine and 2 g (34 mmol) of acetone
 was refluxed for 2 1/2 hours and the volatiles
10 removed to give 3.6 g of imine, which was reduced
 with 550 mg of sodium borohydride in refluxing
 ethanol. After 1 hr. the volatiles were removed in
 vacuo and the residue partitioned between ether and
 water. The organic layer was dried and concentrated
15 to 3.3 g of (adamant-1-ylmethyl)isopropylamine which
 was suspended in 30 ml of H_2O at 0° and 50% aq H_2SO_4
 added until the suspension was acidic. At this time
 a solution of 1.5 g of sodium nitrite in 10 ml of
 H_2O was added forming a white precipitate. After
20 1 hr. at room temperature the mixture was extracted
 twice with methylene chloride and the organic
 layers dried and concentrated to 4.0 g of nitroso-
 amine which was subsequently reduced with 900 mg
 lithium aluminium hydride in refluxing tetra-
25 hydrofuran for 2 hrs. After cooling, sodium-
 sulfate decahydrate was added until bubbling ceased.
 Filtration and evaporation of the filtrate yielded
 2.7 g of oil which was dissolved in ether and treated
 with HCl. The title compound was obtained in 58%
30 yield by filtration.

mp $263-264^\circ$ (d), (isopropanol)
 nmr ($CDCl_3$ /TFA) δ 3.5 (m, 1H); 2.8 (s, 2H);
 1.3 (d, 6H)

1

Anal calcd for $C_{14}H_{27}N_2Cl$:

C, 64.96; H, 10.51; N, 10.82; Cl, 13.72

Found: C, 64.70; H, 10.64; N, 10.71; Cl, 13.50.

Example 39

5

1-[(Adamant-1'-ylmethyl)methylaminolpyrrolidine
hydrochloride

10

To a solution of 1.7 g (7.3 mmol) of 1-(adamant-1'-ylmethylamino)pyrrolidine in dry tetrahydrofuran under N_2 at 0° was added 6 ml (7.3 mmol) of 1.6 M butyllithium, followed in 5 min. by 0.8 ml (12.4 mmol) of methyl iodide. After 15 min. at room temperature water was added and the mixture concentrated in vacuo and twice extracted with ether. The dried ether layers were combined treated with HCl to give the title compound which was obtained in 45% yield by filtration.

15

mp $227-228^\circ$ (d), (isopropanol/ethyl acetate)
nmr ($CDCl_3$) δ 3.4 (m, 4H); 2.8 (s, 3H);
2.5 (s, 2H)

20

Anal calcd for $C_{16}H_{29}N_2Cl$:

C, 67.44; H, 10.26; N, 9.83; Cl, 12.47

Found: C, 67.18; H, 9.97; N, 9.99; Cl, 12.36.

Example 40

25

1-(Adamant-1'-ylmethyl)-2-isopropylhydrazine
hydrochloride

30

A methanolic solution of 1.4 g (6.5 mmol) of adamant-1-ylmethylhydrazine hydrochloride and 1 g (17 mmol) of acetone was refluxed for 4 hrs. The resulting hydrazone was reduced with sodium cyanoborohydride in ethanol. After 1 hr the reaction was basified with 10% NaOH, concentrated, and the residue partitioned between water and methylene chloride. The dried organic phase was concentrated

1 dissolved in ether and treated with HCl. The title
compound was obtained in 25% yield by filtration.

mp 237-242° (ethylacetate/methanol)

nmr (CDCl₃/TFA) δ 3.5 (m, 1H); 2.6 (s, 2H);

5 1.4 (d, 6H)

Anal calcd for C₁₄H₂₇N₂Cl:

C, 64.99; H, 10.44; N, 10.83; Cl, 13.75

Found: C, 64.94; H, 10.17; N, 10.91; Cl, 13.30.

Example 41

10 1-(Adamant-1'-ylmethylamino)-3-methylpyrrolidine
hydrochloride hemi-hydrate

A solution of 1.1 g (6.1 mmol) of adamant-1-ylmethylhydrazine and 700 mg (6.1 mmol) of methylsuccinic anhydride was refluxed in toluene with
15 continuous removal of water via a Dean-Stark
apparatus. After 2 1/2 hrs the solution was diluted
with ether, washed with saturated sodium carbonate,
dried and concentrated to 1.1 g succinimide, which
was reduced with 400 mg of lithium aluminium hydride
20 in refluxing tetrahydrofuran for 3 hrs at which
time the suspension was cooled and sodium sulfate
decahydrate added until bubbling ceased. The
mixture was then filtered and the filtrate concentra-
ted and dissolved in ether and treated with HCl. The
25 title compound was obtained in 22% yield by filtration.

mp 210-215° (d), (ethylacetate)

nmr (CDCl₃) δ 8.2 (m, 3H, exch); 3.0-3.9 (m, 4H);

2.9 (s, 2H); 1.2 (d, 3H)

Anal calcd for C₁₆H₃₀N₂ClO_{1/2}:

30 C, 65.37; H, 10.28; N, 9.53

Found: C, 65.39; H, 10.28; N, 9.91.

1 In the following test results are given
which demonstrate the antimicrobial, antiprotozoan,
CNS, antifungal and antiviral activities of
compounds according to the invention.

5 Antimicrobial activity was demonstrated on
mycoplasma; antiprotozoan activity on Leishmania
and Trypanosoma; CNS activity on albino rats and
albino mice; antifungal activity on human fungi and
yeast; and antiviral activity on HSV-1 (Herpes
10 Simplex) and on influenza virus.

 The following are the results:

1

ANTIMYCOPLASMA ACTIVITY

Some of the compounds were tested against 4 mycoplasma. The method used was as follows:

5

Microorganisms: 1. M. gallisepticum
2. M. capricolum
3. M. hominis
4. A. laidlawii

Assay:

50% inhibition of growth in liquid medium.

10

Results:

The tested compounds of Examples Nos. 3, 7, 8, 38, 25, were found to show a 50% inhibition in concentrations between 5 - 30 µg/ml, which are within the range of antibiotic activity.

1

ANTI LEISHMANIA AND ANTI TRYPANOSOMA TESTS

A. Scoring of drug activity:

1. L. tropica

5

a. amastigotes in peritoneal exudate cells
in Mc Coy's medium in vitro at 37° C.

+++ = clearance of all parasites in 24 hrs

++ = clearance of all parasites in 48 hrs

+ = clearance of all parasites in 72 hrs

10

+ = partial clearance of parasites in
72 hours or more

- = no activity against parasites.

b. promastigotes in Mc Coy's medium in vitro
at 27° C.

15

+++ = no viable parasites after 24 hours

++ = no viable parasites after 48 hours

+ = no viable parasites after 72 hours

+ = no viable parasites after 96 hours

- = viable parasites after 120 hours.

11. Trypanosoma in vitro

20

Trypanosoma in RPMI medium in vitro at 37° C.
Scoring as in b.

1 ANTI LEISHMANIA AND ANTI TRYPANOSOMA TESTS

Results:

		Leishmania		Trypanosoma			
5	Compound or Ex.No.	Amastigote		Promastigote		in vitro	
		10µg	100µg	10µg	100µg	10 µg	100 µg
	1	+	+	-	+++*	+	+++**
	14	+	++			+++	+++*
	15			-	+++		
10	Control Pentamidine			+++	+++	-	++

* An effect was observed with this drug after 1 h at this concentration. No effect was observed with Pentamidine at this time.

** Slight effect.

15 Summary:

The tested compounds of Examples Nos. 1, 14, 15 were found to be active against Leishmania.

The tested compounds of Examples Nos. 1, 14 were found to be active against Trypanosoma.

1

ANTIPARKINSON ACTIVITY

Male Charles River albino rats, weighing 200-250 g, were used. Catalepsy was produced by haloperidol, 5 mg/kg i.p. The animals were placed with their front paws on a horizontal bar, about 10 cm above the ground, and animals were considered cataleptic if not changing posture for at least 30 sec. Cataleptic animals were injected i.p. with one of the drugs at a dose of 40-80 mg/kg. Catalepsy was estimated again at the intervals indicated.

Drug: Control Symmetrel, Route, i.P., Dose: 80 mg/kg

	<u>Time</u>	<u>Rat 1</u>	<u>Rat 2</u>	<u>Rat 3</u>	<u>rat 4</u>	<u>rat 5</u>
	0	+	+	+	+	+
	45	+	-	-	-	-
15	90	+	-	+	+	-
	110	+	+	-	-	-
	180	+	+	-	-	+
	anticataleptic effect	0/4	2/4	3/4	3/4	3/4
20		Mean maximal effect				2.2/4

1

ANTI PARKINSON
EVALUATION OF ANTICATALEPTIC EFFECT IN RATS

5

10

Male Charles River albino rats, weighing 200-250 g, were used. Catalepsy was produced by haloperidol, 5 mg/kg i.p. The animals were placed with their front paws on a horizontal bar, about 10 cm above the ground, and animals were considered cataleptic if not changing posture for at least 30 sec. Cataleptic animals were injected i.p. with one of the drugs at a dose of 40-80 mg/kg. catalepsy was estimated again at the intervals indicated.

Drug: Compound of Example 7, Route: i.p., Dose: 80 mg/kg

	<u>Time</u>	<u>rat 1</u>	<u>rat 2</u>	<u>rat 3</u>	<u>rat 4</u>	<u>rat 5</u>
	0	+	+	+	+	+
15	45	-	+	+	+	+
	90	+	+	+	+	-
	110	+	+	+	+	-
	180	+	+	+	+	-
20	Anticataleptic effect	1/4	0/4	0/4	0/4	3/4

mean maximal effect 0.8/4

1

STEREOTYPED BEHAVIOUR IN MICE

Male ICR albino mice weighing 25-30 g were put in cages with a metal grid floor, 4 in each cage. Drugs were injected intraperitoneally and stereotyped behaviour (sniffing, biting, repetitive head movement) was evaluated every 30 min.

5

Drug Control Symmetrel Route l.p. Dose 50 mg/kg

	<u>Time (min)</u>	<u>Mouse 1</u>	<u>Mouse 2</u>	<u>Mouse 3</u>	<u>Mouse 4</u>
10	0	0	0	0	0
	30	1	1	1	1
	45	1	1	1	1
	60	2	2	1	1
	90	1	1	2	1
15	120	2	2	2	2
	135	2	2	2	2
	150	2	2	2	2
	180	2	2	2	2
	210	2	2	2	1
20	240	2	2	2	0
Total					
Score		17	17	17	13

Mean Score 16

1 Drug Compound of Example 7 Route I.p. Dose 50 mg/kg

	<u>Time (min)</u>	<u>Mouse 1</u>	<u>Mouse 2</u>	<u>Mouse 3</u>	<u>Mouse 4</u>
	0	0	0	0	0
5	30	2	0	0	0
	45	2	0	1	0
	60	2	0	0	0
	90	2	2	0	0
	120	2	2	0	0
10	135	2	2	0	0
	150	2	2	1	0
	180	1	1	1	0
	210	1	1	2	2
	240	1	1	1	1
15	Total				
	Score	17	11	6	3

Mean Score 9.25

Summary:

20 The tested compound of Example 7 was found to be active.

1

ANTIMYCOTIC ACTIVITY

(Human)

The method for the evaluation was as follows:

Microorganisms:

5

1. *Candida albicans*
2. *Trichophyton rubrum*
3. *Trichophyton mentagrophytes*.

Assay:

10

Concentrations of 10 µg/ml, 50 µg/ml, 100 µg/ml, of each of the tested compounds were mixed in a Sabouraud dextrose agar, on which the test organisms were inoculated.

Evaluation:

15

Control (full growth): ++++
No growth: -

The results are summarized in the following table:

1

ANTI HUMAN FUNGI AND YEAST

Compound of Example No.		Concent. µg/ml	C. albicans	T. rubrum	T. menta grophytes
5	Control	10	++++	++++	++++
		50	++++	++++	++++
		100	++++	++++	++++
10	1. 3	10	++++	+++	+++
		50	++++	++	++
		100	++++	+	++
15	2. 8	10	++++	++++	++++
		50	++++	++	++
		100	++++	±	±
15	3. 16	10	++++	++	+++
		50	++++	+	+
		100	+++	+	±
	4. 38	10	++++	++++	++++
		50	++++	++	±
		100	++++	++	±

Results:

- 20 The results indicate that the tested compounds of Examples 3, 8, 16, 38 demonstrate an activity in the range of 50 - 100 µg/ml.

1 INHIBITION TEST ON HSV REPLICATION

Cells - BSC-1 (Green monkey Kidney)
 Virus - HSV-1 (Herpes Simplex)
 Inoculum - 10 PFU/cell
 5 Medium - DMEM + 10% C.S.

Herpes

J. Levitt & Y. Becker

Virology 31, 129-134 (1967)

10	Compound of Example No.	Concent $\mu\text{g/ml}$	T.L. $\mu\text{g/ml}$ *	% Inhibition **
			Toxic Limit	
	Ex.7	100	50	99.9
		75		98
		50		92
		25		72.5
15	Ex.31	100		97
		50		91
		25		51

* T.L. The highest concentration of compound which is completely not toxic.

20 ** % Inhibition of control infected for some time with same virus PFV with no inhibition.

Results

The tested compounds of Examples 7, 31 were found to inhibit HSV by 96-99% at a concentration of 50-200 $\mu\text{g/ml}$.

25 Anti-influenza virus effects (preliminary results)

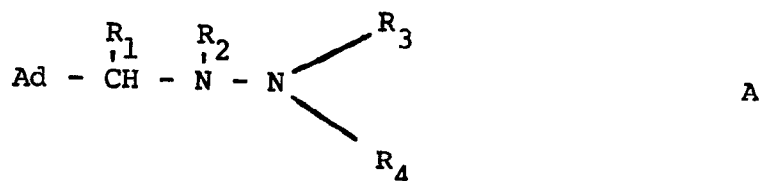
Method :

G. Appleyard and Maber J. of Gen. Virol. 25, 351-357 (1974).

30 The tested compounds of Examples 7, 31, 23, 29, 38, 41, 8 were found effective against influenza A virus at a concentration of 10-50 $\mu\text{g/ml}$.

1 CLAIMS:

1. 1- or 2-Adamantylmethyl hydrazines of the general formula A



5 wherein Ad is 1- or 2-adamantyl, R₁ and R₂ are the same or different and are each hydrogen or a lower unsubstituted or substituted alkyl group of 1-4 carbon atoms; R₃ and R₄ are the same or different and are each hydrogen, an unsubstituted or substituted radical being a lower alkyl of 1-4 carbon atoms, a lower alkanolic acid radical of 2-4 carbon atoms or a lower alkyl ester thereof, adamantyl, aryl, aralkyl in which the alkyl moiety has 1-4 carbon atoms or an unsubstituted or substituted heterocyclic radical of aromatic character; or R₃ and R₄ together with the nitrogen atom to which they are attached form a cyclic radical; and pharmaceutically acceptable acid addition salts thereof.

20 2. 1-(Adamant-1'-ylmethyl)-2-methylhydrazine and pharmaceutically acceptable acid addition salts thereof.

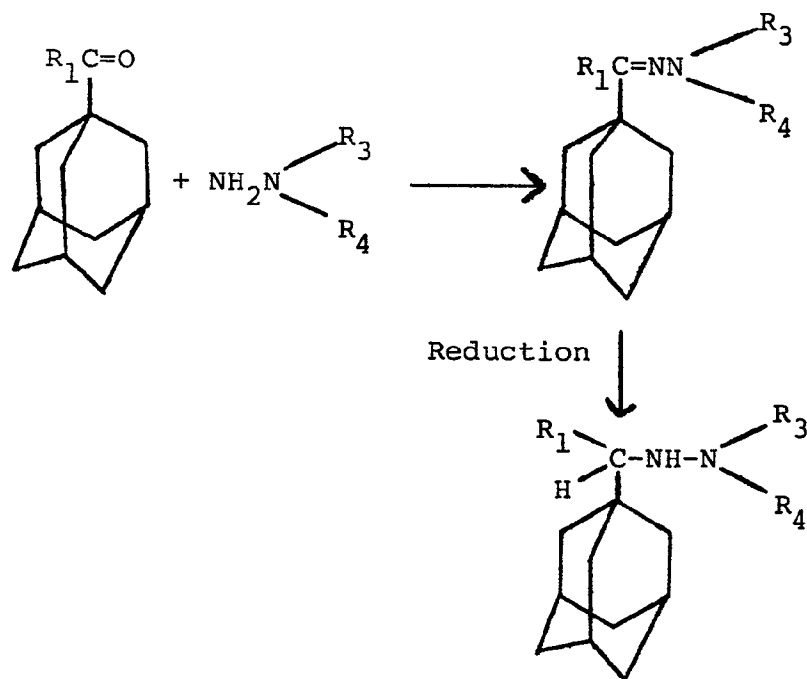
- 1 3. 1-(Adamant-1'-ylmethyl)-2,2-dimethyl-
hydrazine and pharmaceutically acceptable acid addition
salts thereof.
4. 1-(Adamant-1'-ylmethyl)-2-benzylhydrazine
5 and pharmaceutically acceptable acid addition salts
thereof.
5. 1-(Adamant-1'-ylmethyl)-2,2-diphenyl-
hydrazine and pharmaceutically acceptable addition
salts thereof.
- 10 6. 1-(Adamant-1'-ylmethyl)-2-(m-trifluoro-
methylphenyl)hydrazine and pharmaceutically acceptable
acid addition salts thereof.
7. 1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)-
hydrazine and pharmaceutically acceptable acid addition
15 salts thereof.
8. 1-(Adamant-1'-ylmethyldamino)pyrrolidine and
pharmaceutically acceptable acid addition salts
thereof.
9. 1-(Adamant-1'-ylmethyldamino)piperidine and
20 pharmaceutically acceptable acid addition salts thereof.
10. 4-(Adamant-1'-ylmethyldamino)morpholine and
pharmaceutically acceptable acid addition salts thereof.
11. 1-(Adamant-1'-ylmethyldamino)-4-methyl-
piperazine and pharmaceutically acceptable acid
25 addition salts thereof.
12. 1-(Adamant-1'-ylmethyldamino)-4-(m-trifluoro-
methyl)piperazine and pharmaceutically acceptable acid
addition salts thereof.

1 in which R_1 is as in formula A, with a hydrazine
compound in which at least one of the nitrogens does
not bear any substituent to produce the corresponding
hydrazone, and reducing the latter.

5 In the above process the reduction may be
effected in any suitable conventional way, e.g. with
a reducing agent such as sodium cyanoborohydride or
by catalytic hydrogenation using any suitable
conventional hydrogenation catalyst such as, for
10 example, Adam's Catalyst.

The above embodiment for the preparation of
compounds according to the invention is illustrated
in the following Reaction Scheme I in which R_1 , R_3
and R_4 have the same meanings as in formula A and
15 the $R_1C=O$ group is depicted in the 1-position:

Reaction Scheme I



- 1 This general method was applied in
accordance with the invention in the preparation of
the following adamantylmethylhydrazine derivatives:
- 1-(Adamant-1'-ylmethyl)-2-methylhydrazine
- 5 1-(Adamant-1'-ylmethyl)-2,2-dimethylhydrazine
1-(Adamant-1'-ylmethyl)-2-[1"-(2"-hydroxyethyl)]-
hydrazine
1-(Adamant-1'-ylmethyl)-2-benzylhydrazine
1-(Adamant-1'-ylmethyl)-2-phenethylhydrazine
- 10 1-(Adamant-1'-ylmethyl)-2-(p-bromophenyl)hydrazine
1-(Adamant-1'-ylmethyl)-2,2-diphenylhydrazine
1-(Adamant-1'-ylmethyl)-2-(m-trifluoromethylphenyl)-
hydrazine
1-(Adamant-1'-ylmethyl)-2-(o-carboxyphenyl)hydrazine
- 15 1-(Adamant-1'-ylmethyl)-2-[4"-(7"-chloroquinolinyl)]-
hydrazine
1-(Adamant-1'-ylmethyldamino)pyrrolidine
1-(Adamant-1'-ylmethyldamino)-2-methylpyrrolidine
1-(Adamant-1'-ylmethyldamino)piperidine
- 20 1-(Adamant-1'-ylmethyldamino)homopiperidine
1-(Adamant-1'-ylmethyldamino)heptamethylamine
4-(Adamant-1'-ylmethyldamino)morpholine
1-(Adamant-1'-ylmethyldamino)-4-methylpiperazine
1-(Adamant-1'-ylmethyldamino)-4-(m-trifluoromethyl-
- 25 phenyl)piperazine
1-(Adamant-2'-ylmethyl)-2,2-dimethylhydrazine
1-(Adamant-2'-ylmethyl)-2-(pyrid-2"-yl)hydrazine
1-(Adamant-2'-ylmethyldamino)pyrrolidine
1-(Adamant-2'-ylmethyl)-2-(1'-adamantyl)hydrazine
- 30 1-[(Adamant-1'-yl)ethyl] hydrazine
1-[1'-(Adamant-1"-yl)ethyl]-2-methylhydrazine
1-[1'-(Adamant-1"-yl)ethyl]-2-(m-trifluoromethyl-
phenyl)hydrazine

- 1 32. 1-(Adamant-2'-ylmethylamino)-
piperidine and pharmaceutically acceptable acid
addition salts thereof.
- 5 33. 1-(Adamant-2'-ylmethyl)-2-(1"-
adamantyl)hydrazine and pharmaceutically acceptable
acid addition salts thereof.
34. 1-(Adamant-1'-ylmethylamino)thio-
morpholine and pharmaceutically acceptable acid
addition salts thereof.
- 10 35. 1-(Adamant-1'-ylmethylamino)hydantoin
and pharmaceutically acceptable acid addition salts
thereof.
36. 1-(Adamant-1'-ylmethyl)-2-butyl-
hydrazine and pharmaceutically acceptable acid
15 addition salts thereof.
37. α -[2-(Adamant-1'-ylmethyl)hydrazino]-
butanoic acid and pharmaceutically acceptable acid
addition salts thereof.
- 20 38. 1-(Adamant-1'-ylmethyl)-1-isopropyl-
hydrazine and pharmaceutically acceptable acid addit-
ion salts thereof.
39. 1-[(Adamant-1'-ylmethyl)methylamino]-
pyrrolidine and pharmaceutically acceptable acid
addition salts thereof.
- 25 40. 1-(Adamant-1'-ylmethyl)-2-isopropyl-
hydrazine and pharmaceutically acceptable acid
addition salts thereof.

1 41. 1-(Adamant-1'-ylmethylamino)-3-
 methylpyrrolidine and pharmaceutically acceptable acid
 addition salts thereof.

 42. A composition containing as active
5 ingredient a compound according to Claim 1.



European Patent
Office

EUROPEAN SEARCH REPORT

0002065
Application number
EP 78 10 1411

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ²)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>FR - M - 818M</u> (BAYER) * Seiten 1,2 * -----	1,42	A 61 K 31/15 C 07 C 109/00 109/04 C 07 D 295/22 213/77 215/42 233/80
			TECHNICAL FIELDS SEARCHED (Int. Cl. ²)
			C 07 C 109/04 C 07 D 295/22 213/77 215/42 233/80
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<p><input checked="" type="checkbox"/> The present search report has been drawn up for all claims</p>			
Place of search Den Haag		Date of completion of the search 02-02-1979	Examiner FRANCOIS